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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/024,648 | 12/19/2001 | Heather J. Belmont | 49663 (71758) | 2636 |

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT PAPER NUMBER

1632

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

| | | |
|---------------------------------|--------------------------------|--|
| Application No. 10/024,648 | Applicant(s) BELMONT ET AL. | |
| Examiner Anne Marie S. Wehbe | Art Unit 1632 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 24 December 2004 and 18 February 2005.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,2,4-7,9-39 and 41-113 is/are pending in the application.
4a) Of the above claim(s) 9-29,32-37 and 48-111 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,2,4-7,30,31,38,39,41-47,112 and 113 is/are rejected.
- 7) Claim(s) 42-47 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

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DETAILED ACTION

Applicant's amendment and response, the declaration under 37 CFR 1.132 by Heather Belmont, and the supplemental response received on 12/24/04 and 2/18/05 have been entered. Claims 3, 8, and 40 have been canceled. Claims 1-2, 4-7, 9-39, and 41-113 are pending in the instant application. This application contains claims 9-29, 32-37, and 48-111 drawn to an invention nonelected without traverse in the reply filed on 3/29/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 are currently under examination. An action on the merits follows.

Please note that claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 have only been examined to the extent that they read on the elected subject matter, i.e. a transgenic mouse.

The amendment to the claims filed on 12/24/05 is objected to under 37 CFR 1.121(c). The amendment provides a listing of the current status of the claims which does not comply with the requirements of 37 CFR 1.121(c). Claims 38 and 41 are listed as "original"; however, the claims contain markings clearly indicating that these claims are amended. As such, the claims should be followed by the heading "currently amended", see 37 CFR 1.121(c)(2). Furthermore, comparison of claim 38 as amended with original claim 38 shows that additional language, specifically "unrearranged α and β chain human T-cell receptor loci", has been added to the claim which is not appropriately marked as required by 37 CFR 1.121(c)(2). Claim 41 also

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includes additional language not appropriated marked, i.e. "unrearranged". While the amendment has been considered on the merits, please note that future claim amendments must comply with all the requirements of 37 CFR 1.121(c) in order to be considered fully responsive.

Claim Objections

The objection to claims 4-8, 30-31, and 42-47 under 37 CFR 1.75(c) as being in improper form is withdrawn in view of applicant's amendments to or cancellation of the claims. However, please note that the applicant's amendment has resulted in a new ground of objection for claims 42-47 as amended.

Claims 42-47 are newly objected to under 37 CFR 1.75(c) as being in improper form because the claims depend in the alternative on canceled claim 40. Amendment of the claims to remove reference to claim 40 will overcome this objection.

Claim 46 is further objected to for failing to further limit claim 38 or 41 from which it depends. Claims 38 and 41 have been amended to recite that the transgenes comprise unrearranged TCR receptor loci. Therefore, the limitation of claim 46 is redundant and does not further limit either of the parent claims.

Claim Rejections - 35 USC § 103

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The rejection of claims 1-7, 30-31, 38-39, 42-47, and 112 under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, and McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, is withdrawn over claims 1-7, 30-31, 38-39, and 42-47 in view of applicant's amendments to or cancellation of the claims, and **maintained over claim 112**.

The applicant argues that claim 1 has been amended to contain the limitations of claims 3 and 8, and that as claim 8 was not rejected, the rejection should be withdrawn. While this argument was persuasive for claim 1 and claims which depend on claim 1, claim 112 does not depend on claim 1. Claim 112 has not been amended to contain the limitation that the human T cell receptor loci are unrearranged and that the transgenic non-human mammal comprises human alpha and beta chains. Claim 112 continues to read broadly on a transgenic non-human mammal with inactivated endogenous TCR loci comprising a transgene comprising a plurality of human TCR V genes, D genes and/or J and C genes. As such, the rejection of record stands over claim 112 for reasons of record.

Claims 1-2, 5, 7-8, 30-31, 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, and Madsen et al. (1999) Nat. Genetics, Vol. 23, 343-347, is withdrawn in view of applicant's cancellation of or amendments to the claims.

Applicant's amendments have resulted in the following new grounds of rejection under 35 U.S.C. 103(a).

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Claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) *Cell*, Vol. 75, 275-282, McMurry et al. (1997) *Mol. Cell. Biol.*, Vol. 17 (8), 4553-4561, Rowen et al. (1996) *Science*, Vol. 272, 1755-1762, and Rack et al. (1997) *Blood*, Vol. 90(3), 1233-1240.

The applicant claims transgenic mice which comprise human TCR alpha and beta chains, which have inactivated endogenous TCR loci, and whose genome contain transgenes composed of unrearranged human T-cell receptor loci, and methods of making said transgenic mice. The applicant further claims said mice and methods wherein the inactivated loci are endogenous TCR alpha and beta loci, and wherein the endogenous TCR loci have been inactivated by deleting the endogenous D, J, and or C genes.

Littman et al. teaches general methods for producing transgenic non-human animals, preferably mice, which express human lymphocyte transduction proteins and lack expression of the cognate murine lymphocyte transduction protein as a result of inactivation of the endogenous lymphocyte transduction gene loci (Littman et al., abstract, columns 4-6). Littman et al. further teaches that the lymphocyte transduction gene loci and lymphocyte transduction genes include the T cell receptor genes and particularly the T cell receptor alpha and beta gene products (Littman et al., columns 8-9). Littman et al. further provides substantial guidance for making transgenic mice which comprise human lymphocyte transduction transgenes in their genome and which have inactivated cognate lymphocyte transduction transgenes (Littman et al., columns 14-36).

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Littman et al. differs from the instant invention by not specifically describing a transgenic mouse in which the TCR loci are inactivated and human unrearranged TCR V, D and/or J, and C genes have been inserted into the genome. It is noted that although Littman et al. suggests and provides motivation for inactivating the TCR loci of mice and inserting human TCR loci, Littman et al. exemplifies CD4 loci, not TCR loci. However, at the time of filing, transgenic mice which expressed unrearranged human T cell receptor loci and mice which have deletions in the endogenous TCR loci were described and available. Mombaerts et al. for instance teaches 3 different strains of mice which have inactivating deletions in the TCR alpha loci, TCR beta loci, or TCR delta loci (Mombaerts et al., page 275). In particular, note that Mombaerts teaches deleting the D, J, and C genes of the endogenous TCR beta locus (Mombaerts et al., page 3085, Figure 1). Mombaerts et al. also teaches double knock-out mice produced by crossing TCR beta and TCR delta knock-out mice (Mombaerts et al., page 275). McMurry et al. further supplements Littman et al. by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus. McMurry et al. teaches that the human TCR delta gene minilocus comprises unrearranged human multiple V, D, J, and C gene segments (McMurry et al., page 4553-4554). McMurry et al. also teaches that these mice are capable of functionally rearranging the human TCR delta gene locus. In addition, Rowen et al. and Rack et al. supplement the teachings of Littman et al. by teaching the complete 685-kB DNA sequence of the human beta TCR locus and a YAC containing 70% of the TCR alpha locus including multiple TCR alpha V genes, all of the J genes and the C alpha gene respectively (Rowen et al., page 1755-1756, and Rack et al., page 1233-1234 and Figure 1). Therefore, based on teachings and motivation provided by Littman et al. for making transgenic mice which contain human lymphocyte transduction loci, such as the

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TCR alpha and beta loci, and in which the endogenous lymphocyte transduction loci is inactivated, the teachings of Rowen et al. and Rack et al. that nucleic acids encoding the unrearranged human TCR alpha and beta loci were well known, and the teachings of McMurry et al. that transgenic mice comprising unrearranged human TCR loci could be effectively produced and that the human TCR loci were capable of productive rearrangement in mice, it would have been *prima facie* obvious to the skilled artisan to use the nucleic acids taught by Rowen et al. and Rack et al. to make transgenic mice as suggested by Littman et al. and to breed these transgenic mice with any of the TCR loci knock-out mice taught by Mombaerts et al. in order to produce a transgenic mouse in which the endogenous TCR alpha, and/or beta, and/or delta loci are inactivated and which contain the unrearranged human TCR alpha and beta loci. Further, based on the substantial direction provided by all of Littman et al., Mombaerts et al., and McMurry for making transgenic and knock-out mice, the successful demonstration by McMurry et al. that transgenic mice comprising unrearranged human TCR loci can productively rearrange the human loci resulting in functional TCR, and the high level of skill in breeding and crossing mice, the skilled artisan would have had a reasonable expectation of success in making a transgenic mouse comprising an inactivated endogenous TCR loci and comprising human unrearranged TCR alpha and beta loci.

Claim Rejections - 35 USC § 112

The rejection of claims 1-8, 30-31, 38-47, and 112-113 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn in view of applicant's cancellation of claims 3, 8, and 40, and in view of applicant's arguments,

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amendments to the claims, and supporting evidence in the form of the Declaration of Heather Belmont under 37 CFR 1.132 and publications cited in the arguments section of the response.

Applicant's amendments have resulted in the following new grounds of rejection under 35 U.S.C. 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4-7, and 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to recite that the non-human transgenic animal comprises: human alpha and beta chains; inactivated endogenous TCR loci; and transgenes contained within its genome composed of unrearranged human TCR loci. While the claim as amended indicates that the transgenic animal has human alpha and beta chains, it is unclear whether these human alpha and beta chains are intended to refer to human alpha and beta T-cell receptor chains. Many other human proteins comprise alpha and beta chains. As such, clarification is requested. Further, if the applicant intends to claim the expression of human alpha and beta TCR chains, it is unclear from the claim language whether the human alpha and beta chains are encoded by the recited transgenes which comprise unrearranged human TCR loci. Thus, the metes and bounds of the claim cannot be determined as it is unclear whether the human alpha and beta chains recited are

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TCR chain, and further whether the unrearranged TCR loci encoded by the recited transgenes encode human TCR alpha and/or beta loci as opposed to other TCR loci. Claims 2, 4-7, and 30-31 depend from claim 1 and thus are included in this rejection.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the**

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new technology center fax number is (571) 273-8300. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

**ANNE M. WEHBE' PH.D
PRIMARY EXAMINER**

A handwritten signature in black ink, appearing to read 'Anne M. Wehbé', with a long horizontal flourish extending to the right.